
SIDVIM
LIFESCIENCES PVT. LTD.

New Schedule M

A brief summary

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Outline/Background

- Indian Regulatory Authority CDSCO has published a draft version of revised “Schedule M”.
- The objective behind the revision of Schedule M is the harmonisation of quality standards with current global regulatory requirements.
- The harmonisation is similar to the requirements of PIC/s standards.
- This will help many small and medium companies to compete in export markets, regulated markets.
- With the established Schedule M, many companies in India are comply with the basic principle of GMP.
- This new version is designed on a risk-based approach methodology where more emphasis is given to the Quality Risk Management principles and assessments.
- More specific requirements are specified for each activity in the new version compared to the old.

Outline/Background

- These rules shall not apply to the manufacturers, who are presently licensed to manufacture drugs before the 31st October, 2020.
- In rule 74- Conditions of Licence (Form 25 and 25F), clause (o), the word "Good Manufacturing Practices" shall be substituted to the words "Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products".
- In rule 76- Forms of Licences to manufacture drugs in Schs. C and C1 Licence, Sub-rule (8), the word "Good Manufacturing Practices" shall be substituted to the words "Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products".
- In rule 78- Conditions of Licence (Form 28 and 28B or 28D), clause (p), the word "Good Manufacturing Practices" shall be substituted to the words "Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products".

Why INDIA, to join PIC/S ???

- India pharma industry has more than 1,000 CEPs, around 900 approvals across TGA/MCC/ANVISA etc. and around more than 580 sites registered by the USFDA.
- These stats signify that the benefits of Indian Pharma Sector by joining PIC/S will be:
  - Obligatory improvement in India's local GMP inspection system and procedure as well as Quality system requirements.
  - Indian FDA's GMP regulation will be globally accepted after PIC/S compliance.
  - Reduction in inspections and subsequently inspection findings.
  - It will help boost exports.
  - It will help support India's credentials as the best quality manufacturer of pharmaceuticals.
  - It helps in confidence-building through global harmonization of GMP.
  - It apparently upgrades the inspections quality and quality assurance of inspectors.

Old Schedule M

- Schedule M of 2001 is divided in two parts.
- Part I : General Manufacturing Practices for Premises and Materials
  - Each section is explained with certain requirements but not in specific details.
  - Subparts are Part IA to Part IF

    Deals with GMP for Specific product Types.
- Part II- Requirements of Plant and Equipment

1. External Preparations
2. Oral Liquid Preparations
3. Tablets
4. Powders
5. Capsules
6. Surgical Dressing
7. Ophthalmic Preparations
8. Pressurizes and suppositories
9. Inhalers and vitrallae
10. Repacking of Drugs and Pharmaceutical Chemicals
11. Parenteral Preparations

Existing Schedule M Contents

1	General Requirements	15	Self Inspection and Quality Audit	29	Site Master File
2	Warehousing Area	16	Quality Control System	Part I A to Part I F – Specific requirements for manufacture of -	
3	Production Area	17	Specifications	A	Sterile Products, Parental Preparations
4	Ancillary Area	18	Master Formula Records	B	Oral Solid dosage forms
5	Quality Control Area	19	Packaging Records	C	Oral Liquids
6	Personnel	20	Batch Packaging Records	D	Topical Products
7	Health, Clothing and Sanitation for personnel	21	Batch Processing Records	E	Metered Dose Inhalers
8	Manufacturing Operations and Control	22	SOPs and Records	F	Active Pharmaceutical Ingredients
9	Sanitation in manufacturing premises	23	Reference Samples	Part II-	
10	Raw materials	24	Reprocessing and Recoveries		Requirements for Plant and Equipment
11	Equipment	25	Distribution Records		
12	Documentation and Records	26	Validation and Process Validation		
13	Labels and Printed Materials	27	Product Recall		
14	Quality Assurance	28	Complaints and Adverse Reactions		

Proposed Schedule M

- Schedule M of 2018 is divided in XIII Parts
- Part I- Good Manufacturing Practices for Pharmaceutical Products
  - Part I is completely different.
  - This Part I is termed as "Main Principles" & it is mandatory to follow irrespective of product category.
  - An Appendix I which deals with requirements of Site Master File.
- Part II to Part XII
  - Specified requirements for manufacturing, as per product categories. E.g. Sterile products, Oral Solid dosage Forms etc.
  - Five new categories are added as compared to existing Schedule M
- Part XIII
  - Requirements of plant and equipment for manufacturing of 11 categories of pharma products.
  - This section is similar as of previous schedule M 2001.

Proposed Schedule M Contents

1	Pharmaceutical Quality System	14	Premises
2	Quality Risk Management	15	Equipment
3	Good Manufacturing Practices for Pharmaceutical Products	16	Materials
4	Sanitation and Hygiene	17	Reference Standards
5	Qualification and Validation	18	Waste Materials
6	Complaints	19	Documentation
7	Product Recalls	20	Documents Required
8	Change Control	21	Good practices in Production
9	Production under loan licence or contract and contract analysis and other activities	22	Good practices in Quality Control
10	Self Inspection, Quality Audit, Supplier Audit and approval	23	Computerised Systems
11	Personnel	Appendix- I	
12	Training	Site Master File	
13	Personnel Hygiene		

New Schedule M; Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products

Part II to Part XII	
Part II	Specific requirements for manufacture of Sterile Products, Small & Large Volume Parentals, Ophthalmic Preparations
Part III	Specific requirements for manufacture of Hazardous substances such as Sex Hormones, Steroids or Cytotoxic substances (Newly Added)
Part IV	Specific requirements for manufacture of Biological Products (Newly Added)
Part V	Specific requirements for manufacture of Radiopharmaceutical Products (Newly Added)
Part VI	Specific requirements for manufacture of Phytopharmaceutical Products (Newly Added)
Part VII	Specific requirements for manufacture of Investigational Pharmaceutical Products for Clinical Trials in Human (Newly Added)
Part VII	Specific requirements for manufacture of Oral Solid Dosage Forms
Part IX	Specific requirements for manufacture of Oral Liquids
Part X	Specific requirements for manufacture of External Preparations
Part XI	Specific requirements for manufacture of Metered Dose-Inhalers
Part XII	Specific requirements for manufacture of Active Pharmaceutical Ingredients

New Schedule M; Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products

Part XIII	
1	Requirements of Plant and Equipment for External Preparations
2	Requirements of Plant and Equipment for Oral Liquid Preparations
3	Requirements of Plant and Equipment for Tablets
4	Requirements of Plant and Equipment for Powders
5	Requirements of Plant and Equipment for Capsules
6	Requirements of Plant and Equipment for Surgical Dressing
7	Requirements of Plant and Equipment for Ophthalmic Preparations
8	Requirements of Plant and Equipment for Pessaries and Suppositories
9	Requirements of Plant and Equipment for Inhalers and Vitrallae
10	Requirements of Plant and Equipment for Repacking of Drugs and Pharmaceutical Chemicals
11	Requirements of Plant and Equipment for Parental Preparations

Key Aspects; Main Principles

Some of the Key Aspects or Elements of proposed Schedule M

Main Principles: Pharmaceutical Quality System (PQS)

New Schedule M is more specific.

- Section 1 is Pharmaceutical Quality System (PQS)
- Some of the key elements specified in Schedule; but not limited to-
  - GMP should be applied to all stages of product life cycle.
  - It's the responsibility of Senior management to implement effective PQS in the company.
  - There shall be periodic management reviews to identify opportunities for continual improvement of products, processes and PQS itself.
  - A quality manual or an equivalent documentation shall be established and shall contain a description of the quality management system including management responsibilities.
  - Product and process knowledge is managed throughout all lifecycle stages.
  - There is a procedure for self-inspection or quality audit that regularly appraises the effectiveness and applicability of the product quality system.

Main Principles: Pharmaceutical Quality System (PQS)

- Some of the key elements specified but not limited to-
  - The finished product should be correctly processed and checked, according to the defined procedures.
  - All necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations and validations should be in place.
  - There shall be a system for Quality Risk Management.
  - Managerial responsibilities shall be clearly specified in job descriptions.
  - Continual improvement shall be facilitated through the implementation of quality improvements appropriate to the current level of process and product knowledge.
  - Deviations, suspected product defects and other problems should be reported, investigated and recorded.
  - An appropriate level of root cause analysis should be applied during such investigations and appropriate corrective and preventive actions (CAPA) shall be identified.
  - The effectiveness of CAPA should be monitored.

Main Principles: Quality Risk Management (QRM)

- Quality Risk Management is the specific tool to assess the risk and mitigation associated with manufacturing of drug product and drug substance.
- QRM should ensure the risk evaluation of manufacturing process with scientific knowledge, experience.
- QRM can be applied in both the ways, proactively or retrospectively.
- Ultimate goal is the protection of the patient.

Main Principles: Product Quality Review (PQR)

- Regular, periodic or rolling quality reviews of all pharmaceutical products should be conducted.
- Verify the consistency of product process and quality parameters.
- The manufacturer should assess the requirement for re-validation or appropriate CAPA basis the quality review report.
- CAPAs should be completed in timely manner with periodic review of effectiveness check.
- The person who is responsible for release of the product should ensure the quality review is completed within the time specified and should also ensure the accuracy of the data.

Main Principles: Product Quality Review (PQR)

- Product quality reviews shall be conducted and documented annually.
- All the previous reviews shall also be considered during each annual review report.
- Some of the following aspects should be covered in the report, but not limited to-
  - Review of starting materials and packaging materials used for the product
  - The review of supply chain traceability of active substances
  - Review of critical in-process controls, and finished product results
  - A review of all batches that failed to meet established specification and their investigation
  - A review of all changes made to the processes or analytical methods
  - A review of dossier variations submitted, granted or refused
  - A review of the results of the stability monitoring programme and any adverse trends
  - A review of all quality related returns, complaints and recalls and the investigations performed at the time
  - A review of technical agreements to ensure that they are up to date
  - Review of all significant deviations or non-conformances, the related investigations with CAPA effectiveness check.

Main Principles: Good Manufacturing Practices (GMP)

- Good manufacturing practices, an important part of quality management system which ensures quality , safety and efficacy of drug product.
- GMP means quality standards/procedures which ensures-
  - Consistency in process with adequately controlled process parameters
  - Consistency in quality as per product specification
  - Adherence with all the permissions as per regulations
  - Managing and minimizing the associated risks in manufacturing process

Main Principles: Good Manufacturing Practices (GMP)

- Requirements are more specifically mentioned in new Schedule M
- Some of the requirements are as follows-
  - All manufacturing processes are clearly defined, systematically reviewed for associated risks
  - All manufacturing processes shall be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications
  - Qualification and validations are performed.
  - Instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided
  - Procedures are carried out correctly and personnel are trained to do so
  - Manufacture and distribution records should be complete, traceable, comprehensive and accessible
  - A system is available to recall any batch of product from sale or supply
  - Market complaints are to be examined, investigated for defects and appropriate CAPA should be assigned.

Main Principles: Good Manufacturing Practices (GMP)

- All necessary resources are provided, as mentioned below to comply with good manufacturing Practices.
  - Sufficient and appropriately qualified and trained personnel,
  - Adequate premises and space,
  - Suitable equipment and services,
  - Appropriate materials, containers and labels,
  - Approved procedures and instructions,
  - Suitable storage and transport,
  - Adequate personnel, laboratories and equipment for in process controls
  - Books necessary for ensuring compliance with the requirements like Indian Pharmacopeia, Drugs and Cosmetics Act 1940 and other relevant references/guidance documents etc.

Main Principles: Sanitation and Hygiene

- A high level of sanitation and hygiene shall be practiced in every aspect of the manufacture of drugs.
- The scope for Sanitization and hygiene should cover
  - Personnel, Premises
  - Equipments, Production materials, Containers
  - Apparatus, Products for cleaning and disinfection
  - Anything which comes in contact with product
- Potential sources of contamination should be eliminated.
- A programme should be in place for sanitisation and hygiene control.

Main Principles: Qualification and Validation

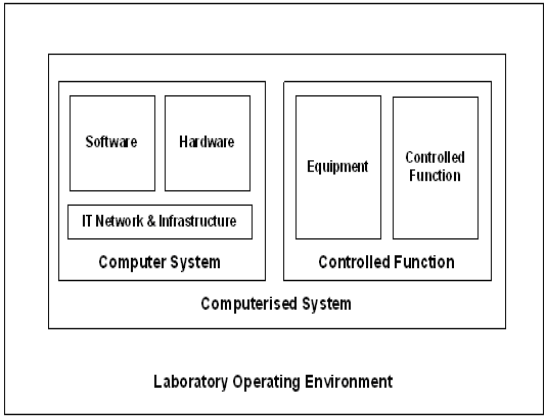
- More specific requirements are cited in new schedule M as compared to old one.
  - Company should identify the process/procedures/equipment/instruments to be addressed by qualification and validation activities.
  - A validation master plan should be in place defining the key elements of qualification / validation programme.
  - Activity should establish and provide the evidence of design qualification (DQ), installation qualification (IQ),operations qualification (OQ) along with performance qualification (PQ) / process validation (PV).
  - Re- validation / re-qualification criteria shall be clearly defined.
  - The responsibility of performing validation activity shall be clearly defined.
  - Particular attention shall be paid to the validation of analytical test methods, automated systems and cleaning procedures.
  - A written report summarizing the results recorded and the conclusions reached shall be prepared and stored.

Main Principles: Production under loan licence or contract and contract analysis and other activities

- One of the major additions in Schedule M.
- Activities performed within specific arrangement, covered by GMP should be clearly defined, agreed and importantly controlled to avoid quality issues.
- There should be a quality contract/ agreement which can take care following activities, not limited to-
  - Tech Transfer, Supply Chain, Subcontracting
  - Validation, Batch Releasing authority, Changes or Changes due to incidents/errors, Quality control, in-process controls etc.
  - Periodic Auditing the activity of site/s, Vendor/s
- Contract acceptor should be aware of all the risks associated with product, work or tests which may affect premises, people, equipment etc.
- Technical aspects of the contract should be drafted by competent persons with suitable knowledge of process technology, analysis and good manufacturing practices.
- All arrangements in manufacturing the product must be in accordance with the licence and agreed upon by both parties.
- All complaints/ any recalls should be properly investigated and approved by both the parties.

Main Principles: Computerised Systems

- Very important section with respect to current approach of regulatory authorities.
- This section is specific about qualification, validation, review, data management associated with computerised system.
- Validation should be based upon complexity, diversity and criticality of system.
- Changes to the computerized system shall be made according to a change procedure with maintaining and authorising all the records.
- These records shall demonstrate that the system is maintained in validated state.
- A back-up system shall be provided so that there is no permanent loss of records due to system breakdown or failure.
- Computerized systems shall have enough controls to prevent unauthorized access or changes to data.
- There shall be a record of any data change made, the previous entry, the person who made the change and when the change was made.
- Written procedures shall be available for the operation and maintenance of computerized systems.



Main Principles: Waste Materials

- There shall be a designated place for proper and safe storage of waste materials.
- Waste materials shall be effectively separated from each other.
- Toxic substances and flammable materials shall be stored in suitably designed, separate, enclosed cupboards.
- The disposal of sewage and effluents (solid, liquid and gas) from the manufacturing area shall be in conformity with the requirements of Environment Pollution Control Board.
- All bio-medical waste shall be destroyed as per the provisions of the Bio-Medical Waste.
- Rodenticides, insecticides, fumigating agents and sanitizing materials shall not be permitted to contaminate equipment, starting materials, packaging materials, in-process materials or finished products.

Synopsis

- If an Organisation of Sterile Injectables, then to comply with Proposed Schedule M, the firm has to follow -
  - Part I- Main Principles
  - Part II- Specific requirements for manufacture of Sterile Products, Small & Large Volume Parental, Ophthalmic Preparations
  - Part III- Requirements of Plant and Equipment for Parental Preparations
- Site Master File – No change in requirements as compared to existing Schedule M.
- With existing established system, organisations have to implement Main principles in the system to comply with Proposed Schedule M.
- Organisation/s shall identify the processes, procedures, systems, equipment etc. which need Quality risk assessment/management to be prepared.
- Risk based data driven decision and approach is the key to implement robust and rugged processes/procedures.

New Additions for Manufacturing Requirements

Specific requirements for manufacture of –

- Hazardous substances such as Sex Hormones, Steroids or Cytotoxic substances- Part III
- Biological Products- Part IV
- Radiopharmaceutical Products- Part V
- Phytopharmaceutical Products- Part VI
- Investigational Pharmaceutical Products for Clinical Trials in Human- Part VII

Thank You!

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